Remarks

Amendment to the Claims

New claims 32 and 33 are added. Basis for these claims is found in the specification as originally filed for example, page 5, lines 14 to 15. No new matter is introduced.

Rejection Under 35 U.S.C. § 102 in view of RALES

Claims 1, 3, 4, 19, and 29-31 were rejected under 35 U.S.C. § 102(b) as being anticipated by RALES investigators, "Effectiveness of *Spironolactone* added to an angiostensin-converting enzyme inhibitor and a loop diuretic for severe chronic congestive heart failure (The Randomized Aldactone Evaluation Study [RALES]" *The American Journal of Cardiology* 78:902-907 (1996)("RALES"). Applicants respectfully traverse this rejection.

Legal Standard

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The fact that a certain result or characteristic ***may*** occur or be present in the prior art ***is not sufficient to establish the inherency of that result or characteristic***. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by

persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). See MPEP § 2112.

Analysis

RALES Fails to Expressly or Inherently Disclose Each Element of the Claims

The Examiner concedes that RALES fails to expressly disclose selecting patients with cachexia and that not all patients with heart failure have cachexia (Office action page 4). The Examiner cites to Freeman et al. *Nutrition Reviews*, 52(10):340-348 (1996) to support the allegation that it was known in the art that cachexia is a common feature in patients with congestive heart failure. In Freeman et al. some congestive heart failure patients having NYHA classes III-IV had 21% lower body weight compared to their "normal" counterparts. The Examiner then suggests that one skilled in the art would conclude that some of the patients in the RALES study would be cachectic because the study included patients classified as NYHA classes II-IV.

The Examiner is applying the wrong standard for inherency. To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill'. The fact that it is theoretically possible that the RALES study included cachectic patients is not sufficient to establish inherency. It is equally theoretically possible that the RALES study did not include cachectic patients. RALES simply does not disclose whether the patients were

cachectic or not. Because the Examiner concedes that not all patients with congestive heart failure are cachectic, the patients in RALES do not necessarily have cachexia. Therefore, RALES cannot inherently anticipate the claimed subject matter.

Moreover, RALES says nothing about the frequency of patients with cachexia. Merely determining weight across a population is not a method of determining whether cachexia has arisen. In a sample group, an overall weight change of zero can be caused by two equal sub-groups of weight-gainers and weight-losers, each gaining or losing 10 kg; or by equal groups gaining and losing 0.1 kg; or by unequal groups gaining and losing different amounts of weight. The overall change in weight of a population relative to controls cannot reveal whether any members of that population are cachectic. It is only by assessing the change of weight of individual patients that the presence or frequency of cachexia can be determined. Contrary to the examiner's assertion, Freeman et al (1994) does not show the presence or the frequency of cachexia in patients having NYHA classes III-IV.

RALES discloses the treatment of heart failure patients with spironolactone and also, as is common in most clinical trials, involves the determination of weight. However, the measurements reported for the RALES trial do not make it possible to tell whether any of the patients treated were cachectic. The time points for weight changes (9 days and 4 weeks after beginning the study medication) are not relevant for an assessment of cachexia. Cachexia is long-term weight loss. As set out in the specification on page 35, lines 7 to 8, cachexia requires the loss of a certain proportion of weight (nominally around 7.5%) over a much longer period of **around 6 months**. Two King et al. papers from 1996 define cachexia as losing at least 6kg

weight loss in the preceding 12 months (copies enclosed). The present inventors have published at least 3 papers using the 7.5% definition in at least 6 months (in Lancet, Circulation and Europ Heart Journal). These are major journals and these papers are peer reviewed, i.e., senior scientists have accepted the definition used by the inventors as appropriate. RALES does not show whether there is cachexia because it does not report weight changes over the long term nor does it stratify the weight changes within individuals. It is not possible to conclude whether patients with cachexia were treated.

Based on the time difference alone, the prior art cannot anticipate the claims, which require weight loss over a period of at least six months because the prior art discloses data over a period of four weeks or less.

In view of the foregoing, RALES cannot inherently anticipate the claimed subject matter because cachectic patients are not necessarily present in this study.

Rejection Under 35 U.S.C. § 102 in view of Packer et al.

Claims 1, 10, 19 and 29-31 were rejected under 35 U.S.C. § 102(b) as anticipated by Packer et al. New England Journal of Medicine, 334:1349-1355 (1996). Applicants respectfully traverse this rejection.

Legal Standard

The legal standard for rejections under 35 U.S.C. § 102 is provided above.

Analysis

Packer et al. Fails to Expressly or Inherently Disclose Each Element of the Claims

The Examiner alleges that Packer et al. anticipates the claimed subject matter because like RALES, some of the patients ***might be*** cachectic. As discussed above, the Examiner is applying the wrong standard for determining inherency. The Examiner conceded that not all congestive heart failure patients are cachectic. This admission alone is sufficient to establish that the cited art does not necessarily include cachectic patients. Packer et al. makes no mention of wasting or weight changes. There is nothing in Packer et al. that allows the skilled person to know whether cachectic patients are included or not.

The patients were observed by Packer over a period of between six and a half and fifteen months but only with respect to cardiovascular symptoms. See the "Safety" paragraph on page 1351, the "Study Procedures" paragraph on page 1350 and the end of the first paragraph of the "Results" section on page 1350. The criteria was survivability, safety, and cardiovascular morbidity. Weight measurement is not referred to although Table 4 on page 1353 indicates that 71 (10%) of patients treated with carvedilol showed weight gain versus 30 (8%) of placebo. This is indicated to be an "adverse reaction". There is nothing in Table 4 to indicate that there is any significant difference in this observed "adverse reaction" between carvedilol and placebo. There is no suggestion whatsoever that the patients who were recognised as experiencing weight gain were cachectic; on the contrary, if the patients were cachectic then the weight gain would not be shown as an "adverse reaction".

Allowance of claims 1, 3, 4, 10, 19-21, and 29-33, as amended, is respectfully solicited.

Respectfully submitted,

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Date: December 11, 2007

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